Etoposide: Drug information

(For additional information see "Etoposide: Patient drug information" and see "Etoposide: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Experienced physician:

Administer etoposide under the supervision of a qualified health care provider who is experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression:

Severe myelosuppression, with resulting infection or bleeding, may occur.

Brand Names: US

Toposar

Brand Names: Canada

Etoposide Injection; Etoposide Injection USP; Vepesid

Pharmacologic Category

Antineoplastic Agent, Podophyllotoxin Derivative; Antineoplastic Agent, Topoisomerase II Inhibitor

Dosing: Adult

US labeling:

Small cell lung cancer (combination chemotherapy):

IV: 35 mg/m^2/day for 4 days, up to 50 mg/m^2/day for 5 days every 3 to 4 weeks

Oral: Due to poor bioavailability, oral doses should be twice the IV dose (and rounded to the nearest 50 mg)

Testicular cancer (combination chemotherapy): IV: 50 to 100 mg/m^2/day for days 1 to 5 **or** 100 mg/m^2/day on days 1, 3, and 5 repeated every 3 to 4 weeks

Canadian labeling: **Non-Hodgkin lymphoma (in combination with other agents), non-small cell lung cancer (alone or in combination), small cell lung cancer (first-line in combination; second-line alone or in combination), testicular cancer (in combination; oral therapy for refractory disease):**

IV: 50 to 100 mg/m^2/day for 5 days

Oral: 100 to 200 mg/m^2/day for 5 days; administer daily doses >200 mg in 2 divided doses.

Adult off-label uses and/or dosing:

Hematopoietic stem cell transplant conditioning regimen, lymphoid malignancies: IV: 60 mg/kg over 4 hours as a single dose 3 or 4 days prior to transplantation (Horning 1994; Snyder 1993; Weaver 1994)

Non-small cell lung cancer: IV: 100 mg/m^2 days 1, 2, and 3 every 3 weeks for 4 cycles or every 4 weeks for 3 to 4 cycles (in combination with cisplatin) (Arriagada 2004) **or** 50 mg/m^2 days 1 to 5 and days 29 to 33 (in combination with cisplatin and radiation therapy) (Albain 2009)

Ovarian cancer, refractory: Oral: 50 mg/m^2 once daily for 21 days every 4 weeks until disease progression or unacceptable toxicity (Rose 1998)

Small cell lung cancer, limited stage: IV: 120 mg/m^2 on days 1, 2, and 3 every 3 weeks (in combination with cisplatin) for 4 courses (Turrisi 1999) **or** 100 mg/m^2 on days 1, 2, and 3 for induction therapy (in combination with cisplatin), followed by consolidation chemotherapy (Saito 2006) **or** 100 mg/m^2 on days 1, 2, and 3 every 3 weeks (in combination with carboplatin) up to a maximum of 6 cycles (Skarlos 2001) **or** 100 mg/m^2 IV on day 1 (in combination with cisplatin), followed by 200 mg/m^2 **orally** on days 2 through 4 every 3 weeks for a maximum of 5 courses (Sundstrom 2002). According to American Society of Clinical Oncology (ASCO) guidelines, platinum-based therapy (cisplatin or carboplatin) in combination with either etoposide or irinotecan for 4 cycles is recommended over other regimens for limited stage disease (Rudin 2015).

Small cell lung cancer, extensive stage: 100 mg/m^2 IV on days 1, 2, and 3 every 3 weeks (in combination with cisplatin) for 4 cycles (Lara 2009) **or** 100 mg/m^2 IV on day 1 (in combination with cisplatin), followed by 200 mg/m^2 **orally** on days 2 through 4 every 3 weeks for a maximum of 5 courses (Sundstrom 2002) **or** IV: 80 mg/m^2 on days 1, 2, and 3 every 3 weeks (in combination with cisplatin) up to 8 cycles (Ihede 1994). According to ASCO guidelines, platinum-based therapy (cisplatin or carboplatin) in combination with either etoposide or irinotecan for 4 to 6 cycles is recommended over other regimens for extensive stage disease (Rudin 2015).

Testicular cancer (combination chemotherapy):

Nonseminoma: IV: 100 mg/m^2/day on days 1 through 5 every 21 days for 3 to 4 courses (Saxman 1998)

Nonseminoma, metastatic (high-dose regimens): IV: 750 mg/m^2/day administered 5, 4, and 3 days before peripheral blood stem cell infusion, repeat for a second cycle after recovery of granulocyte and platelet counts (Einhorn 2007) **or** 400 mg/m^2/day (beginning on cycle 3) on days 1, 2, and 3, with peripheral blood stem cell support, administered at 14- to 21-day intervals for 3 cycles (Kondagunta 2007)

Thymoma, locally advanced or metastatic: IV: 120 mg/m^2 days 1, 2, and 3 every 3 weeks (in combination with cisplatin) for up to 8 cycles (Giaccone 1996)

Unknown primary adenocarcinoma: Oral: 50 mg once daily on days 1, 3, 5, 7, and 9 alternating with 100 mg once daily on days 2, 4, 6, 8, and 10 every 3 weeks (in combination with paclitaxel and carboplatin) (Greco 2000; Hainsworth 2006)

Dosing: Pediatric

(For additional information see "Etoposide: Pediatric drug information")

Note: Oral etoposide is associated with a moderate emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis 2011).

Acute myeloid leukemia (AML) induction (off-label use; combination chemotherapy) (Woods 1996): IV:

<3 years: 3.3 mg/kg/day continuous infusion for 4 days

≥3 years: 100 mg/m^2/day continuous infusion for 4 days

Central nervous system tumors (off-label use; combination chemotherapy): IV:

<3 years: 6.5 mg/kg/dose days 3 and 4 of each 28-day “B” treatment cycle (Duffner 1993)

≥3 years: 100 mg/m^2/day on days 1, 2, and 3 of a 3-week treatment cycle (Taylor 2003)

≥6 years: 150 mg/m^2/day on days 3 and 4 of a 3-week treatment course (Kovnar 1990)

Hematopoietic stem cell transplantation conditioning regimen: IV: 60 mg/kg/dose over 4 hours as a single dose 3 or 4 days prior to transplantation (Horning 1994; Snyder 1993)

Hodgkin lymphoma (off-label use): IV: 200 mg/m^2/day on days 1, 2, and 3 every 3 weeks (Kelly 2002)

Neuroblastoma (off-label use): IV:

Induction: 100 mg/m^2/day on days 1 to 5 of each cycle (Kaneko 2002)

Hematopoietic stem cell transplantation conditioning regimen: 200 mg/m^2/day for 4 days beginning 8 or 9 days prior to transplantation (Kaneko 2002)

Sarcoma, refractory (off-label use): IV: 100 mg/m^2/day on days 1 to 5 of cycle; repeat cycle every 21 days (Van Winkle 2005)

Dosing: Geriatric Refer to adult dosing.

Dosing: Renal Impairment Oral, IV:

The manufacturer’s US labeling recommends the following adjustments:

CrCl >50 mL/minute: No adjustment required.

CrCl 15 to 50 mL/minute: Administer 75% of dose

CrCl <15 mL minute: Data not available; consider further dose reductions

The following adjustments have also been recommended:

Aronoff, 2007:

Adults:

CrCl 10 to 50 mL/minute: Administer 75% of dose.

CrCl <10 mL minute: Administer 50% of dose.

Hemodialysis: Administer 50% of dose; supplemental posthemodialysis dose is not necessary.

Peritoneal dialysis: Administer 50% of dose; supplemental dose is not necessary.

Continuous renal replacement therapy (CRRT): Administer 75% of dose.

Children:

CrCl 10 to 50 mL/minute/1.73 m^2: Administer 75% of dose.

CrCl <10 mL minute/1.73 m^2: Administer 50% of dose.

Hemodialysis: Administer 50% of dose.

Peritoneal dialysis: Administer 50% of dose.

Continuous renal replacement therapy (CRRT): Administer 75% of dose and reduce for hyperbilirubinemia.

Janus, 2010: Hemodialysis: Reduce dose by 50%; not removed by hemodialysis so may be administered before or after dialysis

Kintzel, 1995:

CrCl 46 to 60 mL/minute: Administer 85% of dose

CrCl 31 to 45 mL/minute: Administer 80% of dose

CrCl ≤30 mL/minute: Administer 75% of dose

Dosing: Hepatic Impairment

US labeling: There are no dosage adjustments provided in the manufacturer's labeling.

Canadian labeling:

Mild-to-moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling.

Severe impairment: Use is contraindicated.

The following adjustments have also been recommended:

Donelli 1998: Liver dysfunction may reduce the metabolism and increase the toxicity of etoposide. Normal doses of IV etoposide should be given to patients with liver dysfunction (dose reductions may result in subtherapeutic concentrations); however, use caution with concomitant liver dysfunction (severe) and renal dysfunction as the decreased metabolic clearance cannot be compensated by increased renal clearance.

Floyd 2006: Bilirubin 1.5 to 3 mg/dL or AST >3 times ULN: Administer 50% of dose

King 2001; Koren, 1992: Bilirubin 1.5 to 3 mg/dL or AST >180 units/L: Administer 50% of dose

Dosing: Obesity

*American Society of Clinical Oncology (ASCO) Guidelines for appropriate chemotherapy dosing in obese adults with cancer (**Note:** Excludes HSCT dosing):* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

American Society for Blood and Marrow Transplantation (ASBMT) practice guideline committee position statement on chemotherapy dosing in obesity: Utilize actual body weight (full weight) for calculation of body surface area (BSA) for BSA-based dosing and utilize adjusted body weight 25% (ABW25) for mg/kg dosing for hematopoietic stem cell transplant conditioning regimens in adults (Bubalo, 2014).

ABW25: Adjusted wt (kg) = Ideal body weight (kg) + 0.25 [actual wt (kg) - ideal body weight (kg)]

Dosing: Adjustment for Toxicity Oral, IV:

Infusion (hypersensitivity) reactions: Interrupt infusion.

ANC <500/mm^3 or platelets <50,000/mm^3: Withhold treatment until recovery.

Severe adverse reactions (nonhematologic): Reduce dose or discontinue treatment.

WBC 2000-3000/mm^3 or platelets 75,000-100,000/mm^3: Canadian labeling (not in US labeling): Reduce dose by 50%

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, Oral:

Generic: 50 mg

Solution, Intravenous:

Toposar: 100 mg/5 mL (5 mL); 500 mg/25 mL (25 mL); 1 g/50 mL (50 mL) [contains alcohol, usp, polyethylene glycol 300, polysorbate 80]

Generic: 100 mg/5 mL (5 mL); 500 mg/25 mL (25 mL); 1 g/50 mL (50 mL)

Generic Equivalent Available (US) Yes

Administration

Oral etoposide is associated with a low (adults) or moderate (children) emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis 2011; Roila 2016).

Oral: Doses ≤200 mg/day as a single once daily dose; doses >200 mg should be given in 2 divided

doses. If necessary, the injection may be used for oral administration (see Extemporaneously Prepared). Canadian labeling recommends administering capsule on an empty stomach.

IV: Administer standard doses over at least 30 to 60 minutes to minimize the risk of hypotension. Higher (off-label) doses used in transplantation may be infused over longer time periods depending on the protocol. Etoposide injection contains polysorbate 80 which may cause leaching of diethylhexyl phthalate (DEHP), a plasticizer contained in polyvinyl chloride (PVC) tubing. Administration through non-PVC (low sorbing) tubing will minimize patient exposure to DEHP. Etoposide is an irritant; tissue irritation and inflammation have occurred following extravasation; avoid extravasation.

Concentrations >0.4 mg/mL are very unstable and may precipitate within a few minutes. For large doses, where dilution to ≤0.4 mg/mL is not feasible, consideration should be given to slow infusion of the undiluted drug through a running normal saline, dextrose or saline/dextrose infusion; or use of etoposide phosphate. Due to the risk for precipitation, an inline filter may be used; etoposide solutions of 0.1 to 0.4 mg/mL may be filtered through a 0.22 micron filter without damage to the filter; etoposide solutions of 0.2 mg/mL may be filtered through a 0.22 micron filter without significant loss of drug.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration. For IV preparation, NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs). Double gloving, a gown, and (if dosage form allows) CSTDs are required during IV administration (NIOSH 2016).

Use

Small cell lung cancer (oral and IV): Treatment (first-line) of small cell lung cancer (SCLC)

Testicular cancer (IV): Treatment of refractory testicular tumors (injectable formulation)

Canadian labeling: Treatment of small cell lung cancer (SCLC; first- and second-line); treatment of non-small cell lung cancer (NSCLC); treatment of non-Hodgkin lymphomas (first-line); treatment of testicular cancer (first-line [injectable formulation] and refractory)

Use: Off-Label

Acute myeloid leukemia (AML) induction (Children); Central nervous system tumors; Hematopoietic stem cell transplant conditioning regimen (Children); Hematopoietic stem cell transplant conditioning regimen,

lymphoid malignancies; Hodgkin lymphoma (Children); Neuroblastoma (Children); Non-small cell lung cancer; Ovarian cancer, refractory; Sarcoma, refractory (Children); Thymoma, locally advanced or metastatic; Unknown primary adenocarcinoma; Acute lymphocytic leukemia (ALL); Acute myeloid leukemia (AML), refractory; Breast cancer, recurrent or metastatic; Ewing's sarcoma; Gestational trophoblastic disease; Merkel cell cancer; Multiple myeloma, refractory; Neuroendocrine tumors (adrenal gland and carcinoid tumors); Non-Hodgkin lymphomas; Osteosarcoma; Prostate cancer; Retinoblastoma; Soft tissue sarcoma, metastatic; Thymic malignancies (locally advanced or metastatic); Wilms' tumor

Medication Safety Issues

Sound-alike/look-alike issues:

Etoposide may be confused with teniposide

Etoposide may be confused with etoposide phosphate (a prodrug of etoposide which is rapidly converted in the plasma to etoposide)

VePesid may be confused with Versed

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

The following may occur with higher doses used in stem cell transplantation: Alopecia, ethanol intoxication, hepatitis, hypotension (infusion-related), metabolic acidosis, mucositis, nausea and vomiting (severe), secondary malignancy, skin lesions (resembling Stevens-Johnson syndrome).

>10%:

Dermatologic: Alopecia (8% to 66%)

Gastrointestinal: Nausea and vomiting (31% to 43%), anorexia (10% to 13%), diarrhea (1% to 13%)

Hematologic & oncologic: Leukopenia (60% to 91%; grade 4: 3% to 17%; nadir: 7 to 14 days; recovery: by day 20), thrombocytopenia (22% to 41%; grades 3/4: 1% to 20%; nadir: 9 to 16 days; recovery: by day 20), anemia (≤33%)

1% to 10%:

Cardiovascular: Hypotension (1% to 2%; due to rapid infusion)

Central nervous system: Peripheral neuropathy (1% to 2%)

Gastrointestinal: Stomatitis (1% to 6%), abdominal pain (≤2%)

Hepatic: Hepatotoxicity (≤3%)

Hypersensitivity: Anaphylactoid reaction (intravenous: 1% to 2%; oral capsules: <1%; including bronchospasm, chills, dyspnea, fever, tachycardia)

<1%, postmarketing, and/or case reports: Amenorrhea, apnea (hypersensitivity-associated), back pain, constipation, cortical blindness (transient), cough, cyanosis, diaphoresis, drowsiness, dysphagia, erythema, esophagitis, extravasation (induration/necrosis), facial swelling, fatigue, fever, hyperpigmentation, hypersensitivity reaction, interstitial pneumonitis, ischemic heart disease, laryngospasm, maculopapular rash, malaise, metabolic acidosis, mucositis, myocardial infarction, optic neuritis, ovarian failure, pruritic erythematous rash, pruritus, pulmonary fibrosis, radiation-recall phenomenon (dermatitis), reversible posterior leukoencephalopathy syndrome (RPLS), seizure, skin rash, Stevens-Johnson syndrome, tongue edema, toxic epidermal necrolysis, toxic megacolon, urticaria, vasospasm, weakness

Contraindications

Hypersensitivity to etoposide or any component of the formulation

Canadian labeling: Additional contraindications (not in US labeling): Severe leukopenia or thrombocytopenia; severe hepatic impairment; severe renal impairment

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: **[US Boxed Warning]: Severe dose-limiting and dose-related myelosuppression with resulting infection or bleeding may occur.** Treatment should be withheld for platelets <50,000/mm^3 or absolute neutrophil count (ANC) <500/mm^3.

• Gastrointestinal toxicity: Oral etoposide is associated with a low (adults) or moderate (children) emetic potential; antiemetics may be recommended to prevent nausea and vomiting (Dupuis 2011; Roila 2016).

• Hypersensitivity reaction: May cause anaphylactic-like reactions manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. In addition, facial/tongue swelling, coughing, chest tightness, cyanosis, laryngospasm, diaphoresis, hypertension, back pain, loss of consciousness, and flushing have also been reported less commonly. Incidence is primarily associated with intravenous administration (up to 2%) compared to oral administration (<1%). Infusion should be interrupted and medications for the treatment of anaphylaxis should be available for immediate use. High drug concentration and rate of infusion, as well as presence of polysorbate 80 and benzyl alcohol in the etoposide intravenous formulation, have been suggested as contributing factors to the development of hypersensitivity reactions. Etoposide intravenous formulations may contain polysorbate 80 and/or benzyl alcohol, while etoposide phosphate (the water soluble prodrug of etoposide) intravenous formulation does not contain either vehicle. Case reports have suggested that etoposide phosphate has been used successfully in patients with previous hypersensitivity reactions to etoposide (Collier 2008; Siderov 2002).

• Hypotension: Hypotension may occur due to rapid administration; infuse slowly over at least 30 to 60 minutes. If hypotension occurs, interrupt infusion and administer IV hydration and supportive care; decrease infusion upon reinitiation.

• Secondary malignancies: Secondary acute leukemias have been reported with etoposide, either as monotherapy or in combination with other chemotherapy agents.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dosage should be

adjusted. Canadian labeling contraindicates use in severe impairment.

• Hypoalbuminemia: Use with caution in patients with low serum albumin; may increase risk for toxicities.

• Renal impairment: Use with caution in patients with renal impairment; dosage should be adjusted. Canadian labeling contraindicates use in severe impairment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Elderly: Use with caution in elderly patients; may be more likely to develop severe myelosuppression and/or GI effects.

• Pediatric: The use of concentrations higher than recommended were associated with higher rates of anaphylactic-like reactions in children.

Dosage form specific issues:

• Alcohol: Injectable formulation contains alcohol (~33% v/v); may contribute to adverse reactions, especially with higher etoposide doses.

• Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse (AAP ["Inactive" 1997]; CDC 1982); some data suggests that benzoate displaces bilirubin from protein binding sites (Ahlfors 2001); avoid or use dosage forms containing benzyl alcohol with caution in neonates. See manufacturer's labeling.

• Polysorbate 80: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals (Isaksson 2002; Lucente 2000; Shelley 1995). Thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates after receiving parenteral products containing polysorbate 80 (Alade 1986; CDC 1984). See manufacturer's labeling.

Other warnings/precautions:

• Administration: Must be diluted; do not give IV push, infuse over at least 30 to 60 minutes; hypotension is associated with rapid infusion. Etoposide is an irritant; tissue irritation and inflammation have occurred following extravasation. Do not administer IM or SubQ.

• Experienced physician: **[US Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Metabolism/Transport Effects

Substrate of CYP1A2 (minor), CYP2E1 (minor), CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction

potential; **Inhibits** CYP2C9 (weak)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Aprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Atovaquone: May increase the serum concentration of Etoposide. Management: Consider separating the administration of atovaquone and etoposide by at least 1 to 2 days. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CycloSPORINE (Systemic): May decrease the metabolism of Etoposide. Management: Consider reducing the dose of etoposide by 50% if the patient is receiving, or has recently received, cyclosporine. Monitor for increased toxic effects of etoposide if cyclosporine is initiated, the dose is increased, or it has been recently discontinued. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Etoposide. Management: When possible, seek alternatives to strong CYP3A4-inducing medications in patients receiving etoposide. If these combinations cannot be avoided, monitor patients closely for diminished etoposide response. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates. Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

MiFEPRIStone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. *Risk D: Consider therapy modification*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Etoposide may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Fetal growth restriction and newborn myelosuppression have been observed following maternal use of regimens containing etoposide during pregnancy (NTP 2013; Peccatori 2013). The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). In general, if chemotherapy is indicated, it should be avoided during in the first trimester, there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation. Guidelines for the treatment of SCLC are not provided (Peccatori 2013).

In women of reproductive potential, product labeling for etoposide phosphate notes that it may cause amenorrhea, infertility, or premature menopause; effective contraception should be used during therapy and for ≥6 months after the last dose. In males, azoospermia, oligospermia, or permanent loss of fertility may occur. In addition, spermatozoa and testicular tissue may be damaged. Males with female partners of reproductive potential should use condoms during therapy and for ≥4 months after the last dose.

Breast-Feeding Considerations

Etoposide is excreted in breast milk. Based on data from one case report, concentrations are below the limit of detection 24 hours after the last dose (Azuno 1995). Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

Monitoring Parameters

CBC with differential; liver function (bilirubin, ALT, AST), albumin, renal function tests; vital signs (blood pressure); signs of an infusion reaction

Mechanism of Action

Etoposide has been shown to delay transit of cells through the S phase and arrest cells in late S or early G_2 phase. The drug may inhibit mitochondrial transport at the NADH dehydrogenase level or inhibit uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide does not inhibit microtubular assembly.

Pharmacodynamics/Kinetics

Absorption: Oral: Significant inter- and intrapatient variation

Distribution: Average V_d: Children: 10 L/m^2; Adults: 7 to 17 L/m^2; poor penetration across the blood-brain barrier; CSF concentrations <5% of plasma concentrations

Protein binding: 94% to 98%

Metabolism: Hepatic, via CYP3A4 and 3A5, to various metabolites; in addition, conversion of etoposide to the O-demethylated metabolites (catechol and quinine) via prostaglandin synthases or myeloperoxidase occurs, as well as glutathione and glucuronide conjugation via GSTT1/GSTP1 and UGT1A1 (Yang, 2009)

Bioavailability: Oral: ~50% (range: 25% to 75%)

Half-life elimination: Terminal: IV: Normal renal/hepatic function: Children: 6 to 8 hours: Adults: 4 to 11 hours

Excretion:

Children: IV: Urine (~55% as unchanged drug) in 24 hours

Adults: IV: Urine (56%; 45% as unchanged drug) within 120 hours; feces (44%) within 120 hours

Pricing: US

Capsules (Etoposide Oral)

50 mg (20): $2008.78

Solution (Etoposide Intravenous)

1 gm/50 mL (50 mL): $149.26

100 mg/5 mL (5 mL): $11.37

500 mg/25 mL (25 mL): $74.63

Solution (Toposar Intravenous)

1 gm/50 mL (50 mL): $91.18

100 mg/5 mL (5 mL): $11.24

500 mg/25 mL (25 mL): $45.59

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Actitop (LK); Cavep (CR, DO, GT, HN, NI, PA, SV); Celltop (FR); Citodox (AR); Cryosid (CR, DO, GT, HN, MX, NI, PA, SV); Ebeposide (SG); Eposide (BD); Eposin (CO, MY, TH, TW, ZW); Epsidox (CL); Etocris (PY); Etonco (MX); Etopa (LK); Etopos (MX); Etoposid (AE, CY, IL, JO, KW, QA); Etoposide (AU, IL, NZ); Etoposide Pierre Fabre (LU); Etoposide Teva (HU); Etoposido (PE);

Etopside (EG); Etopul (ID, PH); Etosid (IN, VE); Etozyd (UA); Fitozyd (UA); Fytosid (ET, VN); Lastet (AE, BG, CL, EG, HK, HU, IN, JO, JP, KR, MY, PE, QA, SA, SG, TH, TW, VN); Lastet-S (KR); Oncosid (LK); Posid (PH); Posyd (ID); Sintopozid (HK); Topaxin (BD); Topo (TH); Tosuben (CR, DO, GT, HN, NI, PA, SV); Vepesid (AR, AT, BE, BR, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GR, HN, IE, IT, JP, LB, MT, NL, NO, PH, PK, PL, PT, RO, RU, SE, SI, SK, TR, TW, UY, ZA); VePesid (AU, HR, LU); Vepeside (FR); Vepsid (EG); VP-Gen (EC, PY); VP-TEC (MX)

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